REMARKS

Claims 1-5 and 17-31 are pending in the present application. Claims 1, 4, 5, 24 and 25 have been cancelled. New claims 32-36 have been added. Upon entry of the present amendment, claims 2, 3, 17-23 and 26-36 will be pending.

As a preliminary matter, claims 4, 5, 24 and 25 were not rejected over the prior art of record. Accordingly, claims 4 and 24 have been rewritten as new independent claims 32 and 34, respectively, and claims 5 and 25 have been rewritten as new claims 33 and 35, respectively. Support for new claim 36 can be found throughout the specification and at, for example, page 44, line 27, page 63, line 25, and Examples 11 and 12. Since the addition of new claim 36 removes issues for appeal (i.e., anticipation), Applicants respectfully request that the new claims be entered into the record. See, M.P.E.P. §714.12.

I. No New Matter Has Been Introduced Into The Specification

The Office Action dated October 11, 2000 asserted that the software items referred to at page 94, line 25 to page 95, line 3 of the specification are deemed essential material to fully enable the broad scope of the invention. In particular, Applicants recite at page 94, line 25 to page 95, line 3 the following:

> The three dimensional structure of a molecular interaction site, preferably of an RNA, can be manipulated as a numerical representation. Computer software that provides one skilled in the art with the ability to design molecules based on the chemistry being performed and on available reaction building blocks is commercially available. Software packages from companies such as, for example, Tripos (St. Louis, MO), Molecular Simulations (San Diego, CA), MDL Information Systems (San Leandro, CA) and Chemical Design (NJ) provide means for computational generation of structures. These software products also provide means for evaluating and comparing computationally generated molecules and their structures. *In silico* collections of molecular interaction sites can be generated using the software from any of the above-mentioned vendors and others which are or may become available

The Examiner then referred Applicants to the following paragraph:

> The incorporation of essential material by reference to a foreign application

> or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167.

Applicants took this passage as an obvious invitation by the Examiner to remedy the alleged improper incorporation by amending the specification to include that which was referred to in the passage cited above. In particular, Applicants amended the specification in the Response filed January 3, 2001 to recite particular names of software packages from the companies referred to in the passage cited above. In effect, Applicants inserted the following sentence into the specification:

> Software packages such as, for example, Sybil/Base (Tripos, St. Louis, MO), Insight II (Molecular Simulations, San Diego, CA), and Sculpt (MDL Information Systems, San Leandro, CA).

Applicants also provided an executed Declaration from Dr. David J. Ecker, an inventor of the claimed subject matter, stating that the software packages to which the specification referred were Sybil/Base, Insight II, and Sculpt. Dr. Ecker also averred that the specification has been amended to reflect the particular names of the software packages and that the amendatory material consists of the same material that was referenced in the specification as filed. Thus, to the extent that the names of the software packages are deemed by the Examiner as essential material improperly incorporated (and Applicants do not necessarily agree with the Examiner's position), Applicants have fully complied with the requirements for entering such names into the specification as set forth in M.P.E.P. §608.01(p). Thus, no new matter has been added.

The Office Action dated April 10, 2001 now asserts that the amendment filed January 3, 2001 is objected to under 35 U.S.C. §132 because it allegedly introduces new matter into the specification. In particular, the Office Action asserts that incorporation of the computer software package names into the specification is new matter. The Office Action further asserts that citation of company name does not indicate to what software is being referred. Applicants submit, however,

that the level of skill in the art is high, and as such, one skilled in the art would readily recognize software packages from each of the companies listed in the specification that would perform functions such as those listed in the specification (e.g., manipulation of the three dimensional structure of a molecular interaction site as a numerical representation, design of molecules based on the chemistry being performed and on available reaction building blocks, computational generation of structures, and evaluating and comparing computationally generated molecules and their structures). Indeed, the declaration of Dr. David J. Ecker avers that the computer software package names are the same as that which was referred to in the specification. The Examiner has presented no evidence that would suggest that one skilled in the art of computer modeling, for example, would not be able to recognize appropriate computer software packages made available by the companies referred to in Applicants' specification.

The Office Action also erroneously asserts that nothing is stated in the specification that the "software performs docking of molecules such as in the DOCK program..." discussed in the previous Office Action. Applicants do not, however, teach that the software disclosed at pages 94, line 25 to page 95, line 3 of the specification was, in fact, used by Applicants to perform docking of molecules, although Applicants do not preclude such use. Indeed, docking of molecules is performed by, for example, the DOCK program, as taught throughout Applicants' specification. The software programs produced by Tripos, Molecular Simulations, and MDL Information Systems, in fact, allow three dimensional representations of molecular interaction sites to be produced from two dimensional nucleotide sequences (i.e., manipulation of the three dimensional structure of a molecular interaction site as a numerical representation, design of molecules based on the chemistry being performed and on available reaction building blocks, computational generation of structures).

In addition, in contrast to the assertion in the Office Action, Applicants are not required to inform one skilled in the art the functions of particular computer software packages. Indeed, the art skilled is familiar with the computer software packages referred to in Applicants' specification and need not be reminded of their capabilities. Indeed, it is established law that a patent need not teach, and preferably omits, that which is well known in the art. *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986); *Spectra-Physics Inc. v. Coherent Inc.*, 3

U.S.P.Q.2d 174, 177 (Fed. Cir. 1987). The Office Action also erroneously requires the Declarant to indicate the function of the software. No such disclosure, however, is required in a Declaration. The only statement required by the Declarant, Dr. David J. Ecker, is that the amendatory material consists of the same material that was referenced in the specification as filed. To the extent that the Examiner erroneously maintains that such functions must be recited, Applicants maintain that the specification teaches that the computer modeling software programs produced by Tripos, Molecular Simulations, and MDL Information Systems allow three dimensional representations of molecular interaction sites to be produced from two dimensional nucleotide sequences (i.e., manipulation of the three dimensional structure of a molecular interaction site as a numerical representation, design of molecules based on the chemistry being performed and on available reaction building blocks, and computational generation of structures).

In the alternative, because the new matter rejection applies only to the names of the computer software packages, Applicants submit that the names of the computer software packages are not essential material. Rather, the names of the computer software packages simply indicate the state of the art in computer modeling software. Further, one skilled in the art having examined Applicants' specification in whole would understand that Applicants referred to Sybyl/Base, Insight II, and Sculpt produced by Tripos, Molecular Simulations, and MDL Information Systems, respectively. Applicants enclose herewith a Declaration of Dr. David J. Ecker stating that one skilled in the art, having examined Applicants' entire specification, would have recognized that the computer software packages produced by Tripos, Molecular Simulations, and MDL Information Systems were Sybyl/Base, Insight II, and Sculpt, respectively. Applicants enclose herewith copies of product information for each of Sybyl/Base, Insight II, and Sculpt obtained from their respective websites. One skilled in the art would have no difficulty recognizing that Applicants' identification of the manufacturer and description of the functions of the software, in fact, corresponded to the particular software in question. In view of this alternate theory, the alleged "new matter" may be cancelled concurrently with the rejection thereof.

In sum, Applicants amendment filed on January 3, 2001 introduced no new matter into the specification and followed procedures outlined in the M.P.E.P. Alternatively, the names of the

computer software packages are not essential material. Accordingly, Applicants respectfully request that the new matter objection be withdrawn.

II. The Claimed Invention Is Not Anticipated

Claims 1-3, 17, 18 and 21-23 stand rejected under 35 U.S.C. §102(a) as allegedly being unpatentable over Chen *et al.*, *Biochemistry*, **1997**, *36*, 11402-11407 (hereinafter, the "Chen reference"). Applicants traverse the rejection and respectfully request reconsideration thereof since the Chen reference fails to teach each and every element recited in the rejected claims.

The Chen reference reports structure-based discovery of ligands that are targeted to double stranded RNA. In particular, the Chen reference reports that a series of lead compounds was generated through a database search for ligands with shape complementarity to the RNA deep major groove. The RNA molecule reported in the Chen reference is entirely complementary with itself, thus having a complete double helical structure with no regions of single stranded RNA. Of more than 400 compounds that were examined graphically and found to fit well into the deep major groove, only 11 compounds were selected for testing. In order to determine the binding site of one of the compounds, lividomycin, ^{19}F-NMR solvent isotope shift measurements were carried out on RNA duplexes containing 5-fluorouracil (FU) (see, page 11405, first column). The Chen reference reports that when FU is incorporated into nucleic acid duplexes, the fluorine atom lies in the major groove providing a probe for binding interactions in that groove. The presence of a tightly bound ligand in the major groove should limit the solvent exposure of the major groove atoms and thereby decrease or eliminate the solvent isotope shift.

A prior art reference anticipates a claim if every element of the claim appears in the prior art reference. *See C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1349, 48 U.S.P.Q.2d 1225, 1230 (Fed. Cir. 1998). Applicants respectfully submit that the Chen reference does not disclose every element of the rejected claims.

Claims 21-23 of the invention recite that a molecular interaction site on the target RNA molecule is identified and a three dimensional representation of the site is compared to a virtual library of compounds. In addition, claims 17 and 18 recite a molecular interaction site within RNA.

Claims 21-23 also recite that the target RNA comprises single-stranded RNA. The Chen reference does not teach a molecular interaction site on a target RNA molecule let alone identification of a molecular interaction site on a target RNA molecule prior to comparing a three dimensional representation of the same to a virtual library of compounds. The Office Action asserts that Applicants arguments presented in the Response filed January 3, 2001 are non-persuasive because:

> [T]he previous office action mailed 10/11/00, pointed to the analysis of 400 molecules, clearly a virtual library of compounds, in silico in a 3-D computer evaluation. Thus, this allegation of applicants is clearly contrary to the factual basis for this rejection and thus non-persuasive.

Office Action at page 6. Applicants further argue that the specification defines molecular interaction sites as "small, usually less than 30 nucleotides, independently folded, functional subdomains contained within a larger RNA molecule." *See*, for example, page 16, lines 1-2 of the specification. The Office Action then focuses on each of the phrases for support of the position taken therein.

The Chen reference does not teach identification of a small, *independently folded*, functional subdomain contained within a target RNA molecule. Rather, the Chen reference reports the use of r(UAAGGAGGUGAU)·r(AUCACCUCCUUA), an RNA duplex for which a crystal structure is available, as a target RNA molecule. The molecular "target site," according to the terminology of the Chen reference, of this duplex was "focused on the central region of base pairs 4-9 in the major groove." *See* page 11402 of the Chen reference. Thus, the Chen reference obtained an RNA duplex that had recently been crystalized and focused their ligand binding studies on the major groove of the central portion of the duplex. In contrast to the Examiner's position, Chen reference does not teach that their "target site" is independently folded and also does not disclose that the site is a functional subdomain of their target RNA molecule. Rather, the Chen reference simply used the *major groove* of a central portion of their target RNA molecule as their target site. The major groove of the central six base-pair region of a twelve base-pair RNA duplex **is not** independently folded and is not a functional subdomain of the duplex. The Examiner's argument that the Chen molecule is independently folded simply because it contains base-pairing and forms a major groove is without

merit. The Examiner is reminded that the RNA molecule reported in the Chen reference is entirely complementary with itself, thus having a complete double helical structure with no regions of single stranded RNA. There is no folding of any portion of the double helical structure that is not dependent on the remainder of the double helical structure.

In addition, at no time does the Chen reference teach that steps that were taken to identify a small, independently folded *subdomain* of their target molecule. The Chen reference does not describe any sort of analysis or experimentation to determine whether the RNA duplex reported therein contained a functional subdomain or determine where that subdomain might be located. The Examiner is requested to particularly point out where the Chen reference points out the location of the subdomain and what function is ascribed to it.

Furthermore, claims 21-23 recite that the target RNA comprises single-stranded RNA. Nowhere does the Chen reference report a molecular interaction site on single-stranded RNA. Indeed, the Chen reference, at most, reports RNA in the form of a double helix. Thus, claims 21-23 are not anticipated by the Chen reference.

In addition, new claim 36 recites that an interaction between the compound identified and the molecular interaction sites modulates a function of the target RNA. The Chen reference does not teach or suggest identification of compounds that modulate the function of any RNA. Indeed, the Chen reference selects compounds that associate with the major groove. It is well known that an association with the major groove does not alter RNA function. Thus, new claim 36, and claims dependent thereon, are not anticipated by the Chen reference.

Thus, the Chen reference **does not** teach identification of a molecular interaction site on their target nucleic acid duplex. Indeed, Applicants arguments are fully supported and factually based upon Applicants' specification and the Chen reference. Therefore, the Chen reference does not teach every element of claims 2, 3, 17, 18, 21-23 and 36. Accordingly, Applicants respectfully request that rejection under 35 U.S.C. §102(a) be withdrawn.

III. The Claims Are Enabled

Claims 1-5 and 17-31 continue to be rejected under 35 U.S.C. §112, first paragraph because

the specification allegedly does not reasonably enable the general discovery of molecular interaction sites in macromolecules. Applicants traverse the rejection and respectfully request reconsideration thereof because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

The Office Action dated October 11, 2000 stated that modeling software that allows three dimensional representations of molecular interaction sites to be produced from two dimensional nucleotide sequences is necessary in order to fully enable the invention, and therefore may not be incorporated by reference. To the extent that the Examiner continues to deem the names of the computer software programs as essential material, Applicants have amended the specification, as suggested in the Office Action and as indicated in the passage cited at page 5 of the present Office Action, to incorporate the names of specific software modeling packages made available by the companies recited in the specification at page 94, lines 29-31, which can be used to produce three dimensional representations of molecular interaction sites. Alternatively, as stated above, the names of the computer software packages are not essential material given that Applicants identify the companies, location of companies, and the descriptions of the functions of the computer software packages in the specification as filed. Further, in view of the Declaration of Dr. David J. Ecker, one skilled in the art would have recognized that Applicants were referring to the particularly named computer software packages. Thus, Applicants respectfully submit that the specification, as filed, enables the skilled artisan to make and use the claimed invention without undue experimentation. The specification is commensurate in scope with the claims because the specification teaches the skilled artisan several different means for producing three dimensional representations of two-dimensional molecular interaction sites. The skilled artisan would not have to engage in undue experimentation in order to produce a three dimensional representation of a molecular interaction site from a two-dimensional nucleotide sequence. Accordingly, Applicants respectfully request that the rejection under §112, first paragraph be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for

allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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Date: 14 JUNE 2001

Enclosure: Declaration of Dr. David Ecker; product information for Sybyl/Base, Insight II and Sculpt

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2 has been amended as follows.

2. (Amended) The method of claim [1] 36 further comprising synthesizing the highly ranked members of said hierarchy of compounds.

Claims 1, 4, 5, 24 and 25 have been cancelled.

New claims 32-36 have been added.